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<p>(21) International Application Number: <b>PCT/EP93/00028</b> (22) International Filing Date: <b>8 January 1993 (08.01.93)</b> (30) Priority data: <b>9200391.2</b>      <b>9 January 1992 (09.01.92)</b>      <b>GB</b> (71) Applicant (for GB only): <b>HOLMES, Michael, John [GB/GB]; Frank B. Dehn &amp; Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</b> (71) Applicant (for all designated States except US): <b>NYCOMED IMAGING AS [NO/NO]; Nycoveien 2, P.O. Box 4220 Torshov, N-0401 Oslo 4 (NO).</b> (72) Inventors; and (75) Inventors/Applicants (for US only): <b>KLAVENESS, Jo [NO/NO]; Skøyen terrasse 15, N-0276 Oslo (NO). RØNGVED, Pål [NO/NO]; Hovdens vei 13, N-1454 Hellvik (NO). STUBBERUD, Lars [NO/SE]; Karlskovsvägen 7, S-151 37 Södertälje (SE).</b></p>		<p>(74) Agents: <b>HOLMES, Michael, John et al.; Frank B. Dehn &amp; Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</b> (81) Designated States: <b>AU, CA, FI, JP, NO, NZ, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</b>  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>
<p>(54) Title: <b>IMPROVEMENTS IN CONTRAST AGENTS, CONSISTING OF GALACTOSE PARTICLES</b>  (57) Abstract  Contrast agents comprising water-soluble microbubble-generating carbohydrate microparticles in admixture with at least 10 % w/w relative to the overall composition of a non-surface active material which is less water-soluble than the carbohydrate exhibit useful levels of contrast efficiency and/or stability and may be used in diagnostic applications such as ultrasound and MR imaging.</p>		

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IMPROVEMENTS IN CONTRAST AGENTS,  
CONSISTING OF GALACTOSE PARTICLES.

5           This invention relates to novel contrast agents,  
more particularly to new microparticulate contrast  
agents of use in diagnostic imaging.

          It is well known that ultrasonic imaging comprises  
a potentially valuable diagnostic tool, for example in  
10       studies of the vascular system, particularly in  
cardiography, and of tissue microvasculature. A variety  
of contrast agents has been proposed to enhance the  
acoustic images so obtained, including suspensions of  
solid particles, emulsified liquid droplets, gas  
15       microbubbles and encapsulated gases or liquids. It is  
generally accepted that low density contrast agents  
which are easily compressible are particularly efficient  
in terms of the acoustic backscatter they generate, and  
considerable interest has therefore been shown in the  
20       preparation of gas-containing and gas-generating  
systems.

          Initial studies involving free gas microbubbles  
generated in vivo by intracardiac injection of  
physiologically acceptable substances have demonstrated  
25       the potential efficiency of such bubbles as contrast  
agents in echocardiography; such techniques are severely  
limited in practice, however, by the short lifetime of  
the free bubbles. Interest has accordingly been shown  
in methods of generating and/or stabilising gas  
30       microbubbles for echocardiography and other ultrasonic  
studies, for example using emulsifiers, oils, thickeners  
or sugars.

          Techniques involving the use of sugars in  
ultrasound contrast agents are described in, for  
35       example, US-A-4,681,119, US-A-4,442,843 and US-A-  
4,657,756, which disclose the use of particulate solids  
having a plurality of gas-filled voids and preferably

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also a plurality of nuclei for microbubble formation.  
EP-A-0123235 and EP-A-0122624 suggest ultrasound  
contrast agents consisting of surfactant-coated or  
surfactant-containing gas-containing microparticles  
5 which may include a variety of sugars. DE-A-3834705  
proposes the use of suspensions containing  
microparticles of mixtures of at least one C<sub>10-22</sub> fatty  
acid with at least one non-surface active substance,  
including sugars such as cyclodextrins, monosaccharides,  
10 disaccharides or trisaccharides, as well as other  
polyols and inorganic and organic salts.

Gas-containing contrast media are also known to be  
effective in magnetic resonance (MR) imaging, e.g. as  
susceptibility contrast agents which will act to reduce  
15 MR signal intensity. Oxygen-containing contrast media  
also represent potentially useful paramagnetic MR  
contrast agents.

Furthermore, in the field of X-ray imaging it has  
been observed that gases such as carbon dioxide may be  
20 used as negative oral contrast agents.

A disadvantage of many existing gas-containing/gas-  
generating particulate contrast agents such as the  
sugar-based agents discussed above is their relative  
lack of stability in vivo. This is a particular problem  
25 in applications such as echocardiography, where there is  
a need for improved contrast agents combining sufficient  
stability and small microbubble size (typically less  
than about 10  $\mu$ m, preferably less than about 7  $\mu$ m) to  
permit passage through the pulmonary capillary bed and  
30 so allow enhanced visualisation of the left side of the  
heart, preferably for more than one passage of  
circulation. There is accordingly a need for contrast  
agents which generate microbubble systems exhibiting  
good stability while still providing an effective level  
35 of contrast efficiency.

The present invention is based on our finding that  
contrast agents comprising microparticles of a water-

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soluble carbohydrate admixed with a substantial proportion (e.g. at least 10% w/w relative to the overall composition) of a less water-soluble non-surface active material may be used to generate microbubble systems exhibiting useful levels of contrast effect and/or stability. In the ultrasound field this may be demonstrated by, for example, in vitro measurements of initial attenuation levels and the half lives of the attenuative effect; a useful indication of the combined effect of these properties is the integral obtained by determining the area under the curve of a plot of attenuation against time.

Thus, according to one aspect of the present invention, there are provided contrast agents comprising water-soluble microbubble-generating carbohydrate microparticles in admixture with at least 10% w/w relative to the overall composition of a non-surface active material which is less water-soluble than the said carbohydrate.

The microparticulate carbohydrate may for example be selected from hexoses such as glucose, fructose or galactose; disaccharides such as sucrose, lactose or maltose; pentoses such as arabinose, xylose or ribose; and  $\alpha$ -,  $\beta$ - and  $\gamma$ - cyclodextrins; the term "carbohydrate" as used herein is also intended to embrace sugar alcohols, e.g. alditols such as mannitol or sorbitol. Microparticles of the above carbohydrates will normally have gas present as an inclusion in the voids of their crystal structure and/or adhered to their surface, which gas may generate microbubbles when, for example, the microparticles are suspended or dissolved in an injectable carrier liquid, for example water for injection, an aqueous solution of one or more inorganic salts (e.g. physiological saline or a physiological buffer solution), an aqueous solution of a monosaccharide (e.g. glucose or galactose) or disaccharide (e.g. lactose), or an aqueous solution of a

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physiologically tolerable monohydric or polyhydric alcohol (e.g. ethanol, propanol, isopropanol, ethylene glycol, propylene glycol, glycerine or polyethylene glycol).

5           In addition to or alternatively to air, any biocompatible gas may be employed in the contrast agents of the invention, for example nitrogen, oxygen, hydrogen, nitrous oxide, carbon dioxide, helium, argon, sulphur hexafluoride and low molecular weight optionally  
10 fluorinated hydrocarbons such as methane, acetylene or carbon tetrafluoride. The term "gas" as used herein includes any substance in the gaseous form at 37°C. The gas may be contained in the contrast agent in such a way that before use the product is non-contrast giving but  
15 becomes effective on administration, e.g. as a result of the gas forming microbubbles as the soluble carbohydrate matrix dissolves.

          Additionally or alternatively the carbohydrate may incorporate one or more gas precursors, including  
20 carbonates and bicarbonates (e.g. sodium or ammonium bicarbonate) and aminomalonate esters.

          The non-surface active material may, for example, be a high molecular weight polysaccharide such as starch or dextran which exhibits lower water solubility than  
25 the microbubble-generating carbohydrate; a non-amphiphilic lipid such as a fatty acid ester or steroid acid ester; a fixed oil, fat or wax, for example a partially hydrogenated vegetable oil such as cottonseed oil or soyabean oil or a mixture thereof; a  
30 triglyceride, for example a glyceryl ester of a high molecular weight (e.g. C<sub>10-50</sub>) aliphatic acid, such as glyceryl trilaurate or glyceryl trimyristate; a wax, for example beeswax or carnauba wax; or a mixture of such non-amphiphilic lipids. Alternatively or additionally a  
35 substantially completely water-insoluble material, e.g. an inorganic material such as silica or an iron oxide such as magnetite (Fe<sub>3</sub>O<sub>4</sub>) may be employed.

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As indicated above, the non-surface active material will normally be present in an amount of at least 10% w/w, for example 20-80% w/w, advantageously 25-75% w/w., relative to the overall composition. The

5 microparticulate carbohydrate and non-surface active material may conveniently be employed in substantially identical amounts by weight.

If desired, the contrast agents according to the invention may also contain small amounts (e.g. 0.01-5.0%  
10 w/w, preferably 0.1-2.0% w/w) of materials such as amphiphilic lipids in order to modify the solubility properties of the microparticles. Amphiphilic lipids which may be used for this purpose include fatty acids and salts (e.g. alkali metal salts) thereof, steroid  
15 acids, sterols, phospholipids and glycolipids. The amphiphilic lipid may, for example, be a high molecular weight (e.g. C<sub>10-50</sub>) straight chain saturated or unsaturated aliphatic acid, such as capric, palmitic, hexadecanedioic, stearic, linolenic, behenic,  
20 docosanedioic or melissic acid; an aralkanoic acid, e.g. a phenyl lower alkanoic acid such as 2-phenylbutyric acid; a cholanic acid such as 5 $\beta$ -cholanic acid; salts of any of the foregoing acids; a high molecular weight (e.g. C<sub>10-50</sub>) straight chain aliphatic alcohol such as  
25 stearyl alcohol or cetyl alcohol; a glyceride, for example a glyceryl ester of a high molecular weight (e.g. C<sub>10-50</sub>) aliphatic acid, such as glyceryl monolaurate; cholesterol; a phospholipid such as phosphatidyl choline or dioleoylphosphatidyl.  
30 ethanolamine; or a mixture thereof.

The contrast agents of the invention may be used in a variety of diagnostic imaging techniques, including ultrasound, MR and X-ray imaging. Their use in diagnostic ultrasonic imaging and in MR imaging, e.g. as  
35 susceptibility contrast agents, constitute preferred features of the invention.

The contrast agents of the invention may be



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prepared by any convenient method which leads to physical admixture of the carbohydrate and the less water-soluble non-surface active material and to production of microparticles of the desired size. Thus, for example, the contrast agents may be prepared simply by micronising a mixture of the two components, for example using conventional techniques such as grinding or milling. Alternatively the two components (optionally together with any further component or components such as the above-described lipids) may be mixed in solution, e.g. by mixing an aqueous solution of the carbohydrate and a solution of the less water-soluble non-surface active material in water or a water-miscible organic solvent as appropriate (together with any desired additive, e.g. a lipid dissolved in a water-miscible organic solvent, for example a lower alkanol such as ethanol), the solvent or solvents thereafter being removed (e.g. by evaporation under reduced pressure) to yield a mixture of the desired components which is thereafter micronised to yield the desired microparticles. It will be appreciated that all processing operations should be effected under sterile conditions.

In general micronisation may be effected using conventional techniques such as grinding or milling. Ball-milling has been found to be particularly advantageous, permitting the preparation of microparticles in the form of aggregates (for example having an aggregate size of 20-125 micrometres, such as 30-50 micrometres) of particles having a particle size of, for example, 1-50 micrometres, such as 1-10 micrometres. Such aggregates will tend to contain a substantial volume of air adsorbed on their surfaces and entrained in voids such as interparticle cavities or at grain boundaries between the crystallites. The particle size may, for example, be selected to be substantially commensurate with the desired microbubble size. In

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ultrasonic applications such as echocardiography, in order to permit free passage through the pulmonary system and to achieve resonance with the preferred imaging frequencies of about 0.1-15 MHz, it may be  
5 convenient to employ microbubbles and microparticles having an average size of 0.1-10  $\mu\text{m}$ , e.g. 1-7  $\mu\text{m}$ ; the use of microparticles of average size 1-4  $\mu\text{m}$  to generate microbubbles with an average size of 4-7  $\mu\text{m}$  is generally advantageous. Substantially larger bubbles and  
10 particles, e.g. with average sizes up to 500  $\mu\text{m}$ , may however be useful in other applications, for example gastrointestinal imaging.

The following non-limitative Examples serve to illustrate the invention:-

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Examples 1-3D-(+)-Galactose/Starch Mixtures

D-(+)-Galactose (Merck) in the amounts stated in Table I was mixed with starch (Reppal PSM 70, Reppe Glykos, Sweden) in the stated amounts and ground for 10 minutes under aseptic conditions in a stainless steel ball-mill having a 50 ml grinding cup and 3x20 mm balls (Retsch centrifugal ball-mill, S1).

Table I

Example No.	Amount of D-(+)-galactose (g)	Amount of starch (g)
1	2.0	2.0
2	0.8	3.2
3	3.2	0.8

Example 4D-(+)-Galactose/Iron Oxide Mixture

Commercially available D-(+)-galactose (5.0g) was mixed with commercially available magnetite ( $\text{Fe}_3\text{O}_4$  - 5.0g) and ground in a ball-mill as described in Examples 1-3.

Example 5D-(+)-Galactose/Starch/Palmitic Acid Mixture

D-(+)-Galactose (5.0g) was dissolved in distilled water (7.1g) at 60°C and mixed with starch (5.0g) dissolved in distilled water (30.0g) at 60°C. Palmitic acid (0.02g) was dissolved in 96% ethanol (1.2g) and added with stirring to the carbohydrate solution at 60°C. The solvents were evaporated under reduced pressure (10 torr, 60°C) and the resulting solid mixture was dried in a desiccator overnight prior to being ground in a ball-mill as described in Examples 1-3.

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Examples 6 and 7D-(+)-Galactose/Dextran Mixtures

D-(+)-Galactose in the amounts stated in Table II was dissolved in the stated weights of purified water at 50°C. Dextran (molecular weight ca. 20,000) in the stated amounts was similarly dissolved in the stated weights of purified water at 50°C. The solutions were sterile filtered (0.22  $\mu$ m filter) and mixed with stirring, whereafter the solvent was evaporated under reduced pressure (10 torr, 40°C). The resulting solid mixtures were dried in a desiccator overnight and then ground in a ball-mill as described in Examples 1-3.

Table II

Example No.	Amount of D-(+)-galactose (g)	Weight of water used to dissolve D-(+)-galactose (g)	Amount of dextran (g)	Weight of water used to dissolve dextran (g)
6	5.0	14.4	5.0	14.4
7	2.5	7.2	7.5	21.7

Example 835 Echogenicity in vitro

10 ml of propylene glycol mixed with 90 ml of 5% dextrose in water was used as a carrier liquid for determining the echogenicity of products according to the Examples. 1.0g of each product was dispersed in 3.0 ml of the carrier liquid and shaken for 15 seconds. The resulting mixture was added to 52 ml of 5% human serum albumin infusion solution in the measurement cell and the acoustic effects of the products were investigated by measuring the acoustic transmission through the samples using a 5 MHz broadband transducer in a pulse-reflection technique. The temperature in the measurement cell was stabilised to 37°C and circulation

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of the liquid was maintained by means of stirring at a constant rate. Ultrasound transmission through the samples was measured as a function of time over a duration of 390 seconds. Results were normalized to  
5 measurements on a reference consisting of 55 ml of 5% human serum albumin infusion solution.

The products of the Examples generally showed higher echogenicity than the reference.

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Claims

1. A contrast agent comprising water-soluble microbubble-generating carbohydrate microparticles in admixture with at least 10% w/w relative to the overall composition of a non-surface active material which is less water-soluble than the said carbohydrate.
2. A contrast agent as claimed in claim 1 in which the carbohydrate is a water-soluble pentose, hexose, disaccharide, cyclodextrin or sugar alcohol.
3. A contrast agent as claimed in claim 2 in which the carbohydrate is galactose.
4. A contrast agent as claimed in any of the preceding claims in which the non-surface active material is selected from high molecular weight polysaccharides; non-amphiphilic lipids; fixed oils, fats and waxes; triglycerides; waxes and mixtures of any of the foregoing.
5. A contrast agent as claimed in claim 4 in which the non-surface active material is starch or dextran.
6. A contrast agent as claimed in any of claims 1 to 3 in which the non-surface active material is a water-insoluble inorganic material.
7. A contrast agent as claimed in claim 6 in which the non-surface active material is an iron oxide.
8. A contrast agent as claimed in any of the preceding claims in which the non-surface active material is present in an amount of 25-75% w/w relative to the overall composition.

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9. A contrast agent as claimed in any of the preceding claims additionally containing an amphiphilic lipid so as to modify the solubility properties of the microparticles.

5

10. A contrast agent as claimed in claim 9 containing 0.1-2.0% w/w relative to the overall composition of an amphiphilic lipid selected from fatty acids and salts thereof, steroid acids, sterols, phospholipids and glycolipids.

10

11. A contrast agent as claimed in any of the preceding claims in which the microparticles are aggregates having an aggregate size of 30-50 micrometres of microparticles having a particle size of 1-10 micrometres.

15

12. A process for preparing a contrast agent as claimed in claim 1 which comprises (i) either dry mixing the carbohydrate and the non-surface active material or mixing solutions thereof and removing the solvent(s) therefrom and (ii) micronising the resulting mixture to yield the desired microparticles.

20

13. A process as claimed in claim 12 in which the mixture is micronised by ball-milling.

25

14. Use of a contrast agent as claimed in any of claims 1 to 11 in diagnostic imaging.

15. Use of a contrast agent as claimed in any of claims 1 to 11 in diagnostic ultrasonic imaging.

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16. Use of a contrast agent as claimed in any of claims 1 to 11 in magnetic resonance imaging.

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## INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP 93/00028

<b>I. CLASSIFICATION OF SUBJECT MATTER</b> (If several classification symbols apply, indicate all) <sup>6</sup>		
According to International Patent Classification (IPC) or to both National Classification and IPC		
Int.Cl. 5 A61K49/00		
<b>II. FIELDS SEARCHED</b>		
Minimum Documentation Searched <sup>7</sup>		
Classification System	Classification Symbols	
Int.Cl. 5	A61K	
Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched <sup>8</sup>		
<b>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup></b>		
Category *	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
Y	WO,A,8 502 772 (U. SCHRÖDER & L.G. SALFORD) 4 July 1985 see claims; example ---	1-16
Y	EP,A,0 441 468 (SCHERING A.G.) 14 August 1991 see abstract; claim 11 ---	1-16
Y	AJR AM J ROENTGENOL, VOL. 155, NO. 6, PAGE(S) 1161-7, 1990, WEISSLEDER R ET AL. 'MR receptor imaging: ultrasmall iron oxide particles targeted to asialoglycoprotein receptors.' see abstract; table 1 --- -/--	1-16
<p>* Special categories of cited documents: <sup>10</sup></p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art</p> <p>"&amp;" document member of the same patent family</p>		
<b>IV. CERTIFICATION</b>		
Date of the Actual Completion of the International Search		Date of Mailing of this International Search Report
03 MAY 1993		24.05.93
International Searching Authority EUROPEAN PATENT OFFICE		Signature of Authorized Officer DULLAART A.W.M.



III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
Y	EP,A,0 131 540 (SCHERING A.G.) 16 January 1985 see abstract; examples see claims ---	1-16
Y	CURR OPIN RADIOL, VOL. 3, NO. 2, PAGE(S) 198-207, 1991, SCHLIEF R 'Ultrasound contrast agents.' see page 199 - page 200 see page 205 -----	1-16

**ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.**

EP 9300028  
SA 69413

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report.  
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		SE-A- 8307060	22-06-85
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		JP-A- 60075437	27-04-85
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